WESTERN SYDNEY
UNIVERSITY

Participant Information Sheet

Project Title: Evaluation of the safety and efficacy of medicinal cannabis for endometriosis: A double-blind, randomized, controlled trial.

Project Summary:

You are invited to participate in a research study being lead by Associate Professor Mike Armour. The research team includes Amelia Mardon, Dr Deep Bhuyan and Dr Mitchell Low from Western Sydney University, Assoc Prof George Condous from University of Sydney, Prof Jason Abbott and Dr Cecilia Ng from UNSW, Dr Mathew Leonardi from Robinson Research Institute, University of Adelaide, Prof Kerry Sherman from Macquarie University and Dr Leesa Van Niekerk from University of Tasmania. The research involves participating in a clinical trial that will test 2 medicinal cannabis products for the management of endometriosis.

If you are aged 18 years and older, live in New South Wales, and have a confirmed diagnosis of endometriosis with pelvic pain, you may be eligible to participate in the study. To confirm your eligibility, we will need to ask you more questions before you start.

How is the study being paid for?

This project is funded by a philanthropic donation by The Wilson Foundation.

Why is this study being done?

Endometriosis is a condition where endometrial-like tissue grows outside the uterus. The direct consequences of endometriosis include chronic pelvic pain, heavy menstrual periods, fatigue, impaired quality of life, decreased work productivity, and having to take time off work. Endometriosis has also been consistently associated with mental health issues such as anxiety and depression. Unfortunately many of the pharmaceutical medications for endometriosis have bothersome side effects or should only be used for a short period of time due to concerns related to dependence and addiction. Therefore, it is important to find new treatments that are safe, effective, and with low potential for addiction.

Medicinal cannabis may be effective for the management of endometriosis. This study is designed to test if two medicinal cannabis products can improve endometriosis symptoms compared to a control (a medication that looks like the treatment but doesn't contain any active ingredients). We will also be making sure the treatment is safe by monitoring any side effects you might have.

What will I be asked to do?

After initial assessment and consent, you will be asked to visit a gynaecologist at either Alana Healthcare or Sydney Endometriosis to complete some questions about you (demographics), your medical history, and your health (including pain severity, quality of life, and mental wellbeing). You will also be invited to have a blood test for safety checks (your blood count, liver and kidney function). Once this is complete and if you are eligible, you will be enrolled in the study. You will then be asked to have a transvaginal ultrasound at Sydney Endometriosis to determine the stage of your endometriosis. If you have a "negative" scan (no endometriosis seen via ultrasound), this will not exclude you from participating in the study. For a portion of participants, we will also invite you to complete an online cognitive function test. All ultrasound scans, blood tests, and other investigations during the trial, as well as all trial products, will be provided at no charge.

You will then be randomised (so the research team don't have any control over which treatment you get, and you won't know which one you are getting during the study) to one of the three groups – Luna

Oil (THC and CBD), Elan Oil (CBD only), or a control oil (no active ingredients). The three treatments look and taste the same. Over the first two weeks, you will be asked to slowly increase your treatment dose to see if you experience any side effects. During this time, you will complete a daily log on an app to track your dose, pain, and any side effects.

Throughout the study you will take two doses of oil per day for 26 weeks – one dose in the morning and one dose at night. You will continue to log your pain and symptoms in the app every week whilst you are taking the treatment. At the mid-treatment point and end of the 26 weeks, you will have another blood test (safety checks: your blood count, liver and kidney function, inflammation markers, and cannabis markers), and complete some questionnaires. At the end of the 26 weeks, we will also invite you to undergo another transvaginal ultrasound to see if your endometriosis has changed during this time.

At 6 and 12 months after you stop taking the treatment (oil), we will ask you to fill in some online questionnaires on how you are feeling. Blood tests, body samples, ultrasounds, and online cognitive function tests will also occur. We will also invite some participants to complete an online one-on-one interview to discuss their experiences of the study.

In more detail:

- Baseline visit (30 minutes): after an initial eligibility screening and providing your written consent to participate in the study, you will be asked to attend an appointment with a gynaecologist at either Alana Healthcare or Sydney Endometriosis. to confirm your eligibility and complete questionnaires about you. You will also be asked to register onto the NECST registry so we can track any treatments you use for your endometriosis throughout the trial.
- Safety check (20 minutes): following the appointment with the gynaecologist, you will be asked to have a blood test taken for safety checks (your blood count, liver and kidney function) at a pathology laboratory located near you and this will act as the final check of your eligibility for the study.
- Transvaginal ultrasound (45-60 minutes): Once your blood test demonstrates that your kidney and liver is within safe ranges by a study doctor, you will have a transvaginal ultrasound to look at the size and stage of your endometriosis. This will be done at Sydney Endometriosis.
- Online cognitive function test (60 minutes): For a subset of participants, you will be invited to participate in an online cognitive function test. Someone from the research team will be in contact with you if you are eligible for this test.
- Randomisation: Once your baseline tests have been completed, you will be randomised onto the trial and the oil treatment will be couriered to you.
- Run in period (2 weeks): For the first two weeks of the trial, you will slowly increase your dose of treatment product. You will complete a daily log on an app to track your dose, pain, and side effects. If you do experience any side effects, a member of the research team will contact you to follow up.
- Midpoint (90 minutes): After the first two weeks, you will continue to log your dose and symptoms via an app each week. You will complete a blood test blood test (safety checks: your blood count, liver and kidney function; inflammation markers, and cannabis markers), and provide body samples. We will get you to complete an online questionnaire about yourself. We will also ask you to upload a photo from your phone or tablet showing how much of your treatment you have remaining and send you additional treatment if needed.
- End of treatment (various times): After taking the treatment for 26 weeks, you will be asked to complete multiple tests, including:
    - Online questionnaire asking about your symptoms, quality of life, and mental wellbeing (30 minutes),

  - a blood test (safety checks: your blood count, liver, and kidney function; inflammation markers, and cannabis markers) at your local pathology centre (20 minutes),
  - Transvaginal ultrasound to look at the size and stage of your endometriosis (45-60 minutes). This will be done at Sydney Endometriosis in a subset of participants.
  - Online cognitive functioning via Zoom for a subset of participants (60 minutes).

  We will not be sending you any additional medication as you would have finished the treatment period for the study.

- Post-treatment follow-up 1 (various times): After stopping taking the medication, you will complete a log on an app each month to track your pain and any side effects. Six months after stopping the medication, we will also ask you to:
  - Complete an online questionnaire asking you about your symptoms, quality of life, and mental wellbeing (30 minutes),
  - have a blood test (safety checks: your blood count, liver, and kidney function; inflammation markers, and cannabis markers) at your local pathology centre (20 minutes).
  - have an online cognitive function test via Zoom (60 minutes). This will be done in a subset of participants.

- Post-treatment follow-up 2 (various times): The second follow-up will occur 12 months after stopping the medication and be similar to the first follow-up. You will continue to complete a log on an app each month to track your pain and any side effects. We will also ask you to:
  - Complete an online questionnaire asking you about your symptoms, quality of life, and mental wellbeing (30 minutes),
  - have a blood test (safety checks: your blood count, liver, and kidney function; inflammation markers, and cannabis markers) at your local pathology centre (20 minutes).
  - have transvaginal ultrasound to look at the size and stage of your endometriosis (45-60 minutes). This will be done at Sydney Endometriosis in a subset of participants, and,
  - Participate in an online one-on-one interview held on Zoom, for a subset of participants.

Driving while using products containing THC is illegal in NSW. Under the current laws in NSW, you will not be able to drive or operate heavy machinery during the time you are taking the trial treatments as you won't know if you are in a group that includes THC, so even if you don't feel impaired you should not drive during this time.

How much of my time will I need to give?

The total time you will need to give in this study is approximately 8-9 hours (not including travel time to) that is spread across 18 months.

What kind of treatment will I receive?

There are two treatments being tested in this trial, both are types of medicinal cannabis and both are taken orally, not smoked. The first is one an oil with both THC and CBD in equal amounts. The second is an oil with mostly CBD but very small amounts of THC are also present. Cannabis has been used by people with endometriosis previously, with some people reporting improvements in their pain and other symptoms, but it's unclear what dose is needed to be effective, or how effective it is in the general population who have endometriosis.

We will be testing these treatments against a study medication that looks and tastes the same but doesn't have any of the active ingredients (called the 'control treatment').

Whether you get the active or control treatment is based on randomisation. This means the research team don't know in advance which treatment you will get and your allocation to a treatment group is based purely on chance. You have a greater chance that you will receive an active treatment (66%) compared to the placebo treatment (33%). It is important to note that neither yourself nor the research team will know which treatment (i.e., active or placebo) you have received until after the study finishes. This is referred to as double-blinding.

You will however find out which group you were allocated to (i.e., active or placebo) after the trial has finished **and** after we've preformed the necessary data analysis from the data collected. Please note that finding out which group you've been allocated to (i.e., active or placebo) will **not** occur once you've completed your final post-treatment follow-up but rather once the trial has completed recruitment and analysis of the data collection has concluded. This can take quite a long time, so it might be a year or more after you finish until you find out.

What benefits will I, and/or the broader community, receive for participating?

If you are currently suffering from endometriosis, you may experience an improvement in your endometriosis-related symptoms from taking the study medication, although there is no guarantee this will happen. You will also get a blood test for safety monitoring (i.e. to ensure there is no pre-existing and previously non-identified issues with your liver and kidney functions). You will be reimbursed with a $100 prepaid Mastercard to cover the costs associated with participating in the study.

If the study medication is found to be more effective, compared to the control, for an improvement in endometriosis-related symptoms, this has the potential to benefit people with endometriosis.

Will the study involve any risk or discomfort for me? If so, what will be done to rectify it?

The medicinal cannabis products used in this study is considered safe for oral consumption. The expected adverse event profile of the active treatments is based on its CBD and/or THC content. CBD and THC has been associated with abnormal liver function tests and some side effects include decreased appetite, diarrhoea, and drowsiness.

To monitor for side effects, the research team will monitor you whilst you are taking the medication and the year following. We also will take another blood test at the mid-treatment, end of the trial, and at two follow-up timepoints to compare to your blood results from before you started the medication. Lastly, if you do report any side effects during the study, we will check in on you via telephone call. It is important that if you have any side effects that you are concerned about at any time to contact the research team. If you think they are mild please contact the study staff via the contact details in your app log or at the end of this sheet. If you feel they are serious or life threatening please immediately seek medical attention from your GP or emergency department.

How do you intend to publish or disseminate the results?

We anticipate that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, we will present information in such a way that a participant can't be identified, such as tables and graphs showing the overall information.

We will be providing an easy to read summary of our results to all major endometriosis support organisations in Australia, which they can provide to their members/followers.

If you would like to receive a summary of research results individually, please tick the box on the Consent Form.

Will the data and information that I have provided be disposed of?

Please be assured that only the researchers will have access to the raw data you provide. However, your data may be used in other related projects for an extended period of time.

In accordance with the Australian privacy and other relevant laws, you have the right to request access to your information that we have collected and stored by the research team. Please contact the chief investigator, A/Prof Mike Armour, m.armour@westernsydney.edu.au, if you would like access to your information.

We will store all information collected for this study securely and destroy it 15 years after the results are published in accordance with university policy and the Australian Code for the Responsible Conduct of Research.

Can I withdraw from the study?

Participation is entirely voluntary, and you are not obliged to be involved. If you do participate you can withdraw at any time.

If you choose to withdraw, the study investigator or other staff may ask you for your reason for withdrawing to ensure we follow up on any unresolved issues. If you withdraw, you can advise us that you do not consent for us to use the data we collected up until your withdrawal. We will only use the information that you give consent for us to use.

Whatever your decision, it will not affect your medical treatment or your relationship with the medical or other staff involved in the study.

Can I tell other people about the study?

Yes, you can tell other people about the study by providing them with Amelia Mardon's (Study Clinical Trial Coordinator) details endocanntrial@westernsydney.edu.au. They can then contact Amelia Mardon to discuss their participation in the research project and obtain a copy of the information sheet.

What if I require further information?

Please contact the research team at endocanntrial@westernsydney.edu.au should you wish to discuss the research further before deciding whether to participate.

What if I have a complaint?

If you have any complaints or reservations about the ethical conduct of this research, you may contact the Ethics Committee through Research Engagement, Development and Innovation (REDI) on Tel +61 2 4736 0229 or email humanethics@westernsydney.edu.au.

Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.

If you agree to participate in this study, you may be asked to sign the Participant Consent Form. The information sheet is for you to keep, and the consent form is retained by the researcher/s.

This study has been approved by the Western Sydney University Human Research Ethics Committee. The Approval number is H15755.

What will happen with my information if I agree to it being used in projects other than this one?

Thank you for considering being a participant in a university research project. The researchers are asking that you agree to supply your information (data) for use in this project and to also agree to allow the data to potentially be used in future research projects.

This request is in line with current University and government policy that encourages the re-use of data once it has been collected. Collecting information for research can be an inconvenience or burden for participants and has significant costs associated with it. Sharing your data with other researchers gives potential for others to reflect on the data and its findings, to re-use it with new insight, and increase understanding in this research area.

You have been asked to agree to Extended consent.

Extended consent

When you agree to extended consent, it means that you agree that your data, as part of a larger dataset (the information collected for this project) can be re-used in projects that are

- an extension of this project
- closely related to this project
- in the same general area of this research.

The researchers will allow this data to be used by members of the research team only.

To enable this re-use, your data will be held at the University in its data repository and managed under a Data Management Plan. The stored data available for re-use will not have information in it that makes you identifiable. The re-use of the data will only be allowed after an ethics committee has agreed that the new use of the data meets the requirements of ethics review.

The researchers want to keep the data for 15 years for possible re-use. After this time the data will be securely destroyed.

You are welcome to discuss these issues further with the researchers before deciding if you agree. You can also find more information about the re-use of data in research in the National Statement on Ethical Conduct in Human Research – see Sections 2.2.14 - 2.2.18.

https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018